REMARKS

Claims 10, 11 and 13 to 24 are pending and under examination. In the present communication, claim 11 has been cancelled and claim 10 has been amended. A marked up copy to show changes made is attached herewith as Exhibit A and the claims as they will stand upon entry of the amendments is attached herewith as Exhibit B. .

Rejection Under 35 U.S.C. § 112, first paragraph

The rejection of claims 10-13 to 13, 19 and 22 to 24 under35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully traversed.

Applicants respectfully disagree with the Examiner's assertion that the specification does not reasonably provide enablement for a method for detecting a cellular proliferative disorder in a subject by determining the aberrant methylation state of APOB, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PARA2, PITX2, PTCH, SDC1 and SDC4. As acknowledged by the Examiner, the specification teaches CpG-rich regions from these genes which are methylated (page 7, lines 10-11, Figures 4A -4F). Invention methods, as recited in claim 10, include identifying aberrant methylation of the genes, which "comprises hypermethylated CpG rich regions (i.e., islands)" (Specification, page 30, lines15-16).

Applicants further disagree with the Examiner's assertion that the "specification explicitly teaches that whether large CpG islands are aberrantly methylated in cancer is not apparent (p.24)". It is respectfully submitted that the Examiner has misread the quoted passage. The text referred to says:

> The CACNA1G CpG island is 4 kb, and is larger than many typical CpG islands. MINT31 corresponds to the 5' edge of the island while CACNA1G is in the 3' region. It is not known whether large CpG islands such as this are coordinately regulated with regards to protection from methylation and aberrant methylation in cancer.

It is clear that what was not known is whether there is coordinate regulation of multiple CpG islands in association with disease states. The large CpG island contained in CACNA1G may be divided into multiple regions; the specification discloses that the island is divided into eight regions (page 25, lines 6-7). These islands are aberrantly methylated in cell proliferative disorders. The present disclosure demonstrates that there are five identifiable patterns of methylation with respect to the eight regions in association with certain cell lines (see, page 26, lines 7 to 12).

Furthermore, Applicants respectfully disagree with the Examiner's assertion that the "specification has not provided any correlation between tumor and normal tissue regarding hypermethylation for APOB, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PARA2, PITX2, PTCH, SDC1 and SDC4" such that one of skill in the art would be able used the information to detect cellular proliferative disorders. As indicated in Table 5, each of the genes is methylated in one more cellular proliferative disorders. For example, APOB, HSPA6, IQGAP2 and KL are methylated in common tumors; CDX2, EGFR, GPR37, PAR2, PITX2, PTCH, SDC1 and SDC4are methylated in leukemias; GPR37 and FBN1 are methylated in colon cancers; CDX2, EGFR, FBJN1, GPR37, PAR2 and PITX2 are methylated in breast cancers; and FBN1 and PITX2 are methylated in prostate cancers. It would not require undue experimentation for those of skill in the art to perform the necessary experimentation to determine that the listed genes are hypermethylated in specific tumors and other cellular disorders. Multiple factors are considered in determining whether a disclosure requires "undue experimentation" including (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented,

(3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands, 858 F.2d 731, 735, 736-37(Fed Cir.1988).*

With respect to factors (1) the quantity of experimentation necessary and (2) the amount of direction or guidance presented, it is respectfully submitted that reasonably little experimentation is required to carry out invention methods and that ample direction and guidance is provided by the disclosure. Indeed, the present invention can readily be carried out with little experimentation and the Examiner has acknowledged that a significant amount of guidance is provided by the disclosure. Detailed protocols to assess the methylation status of genes in cancerous and non-cancerous cells are provided in the Examples section. The nucleic acid sequences of gene regions having CpG islands that may be methylated are provided in Figure 4, and primer sequences for amplifying such regions are provided in Table 4. Those skilled in the art at the time of the invention had ample knowledge of how to perform the required assays and ample guidance is provided by the present disclosure to determine that methylation of a particular gene or gene region is associated with a cell proliferative disorder.

With respect to factor (3) the presence or absence of working examples, Example 1 provides a detailed example of invention methods.

With respect to factors (4) the nature of the invention, (5) the state of the prior art, and (6) the relative skill of those in the art, it is respectfully submitted that the present invention pertains to the field of molecular and cellular biology, an established area of scientific endeavor that is practiced by skilled individuals who have a high degree of technical expertise. Moreover, the widely recognized growth in this scientific field during the past 20 years provides a large base

of art related to molecular biological techniques. Applicants respectfully submit that the nature of the invention, the state of the prior art and the relative skill of those in the art are such that undue experimentation would not be required to practice invention methods.

With respect to factor (7) the predictability or unpredictability of the art, it is respectfully submitted that unpredictable factors apply minimally, if at all, to invention methods. Amplification of polynucleotides using specifically identified primers following treatment with chemical agents is a routine skill in the art.

In view of the factors considered, it would not require undue experimentation to determine that a particular gene region is hypermethylated in a cell proliferative disorder. Although the technical work required can be tedious, it is not undue experimentation.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, of claims 10-13, 19, and 22 to 24.

Rejection Under 35 U.S.C. § 102(a)

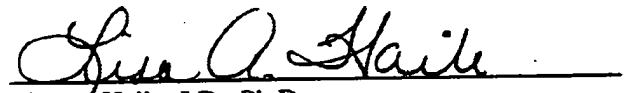
The rejection of claims 10, 11, 13 to 24 under 35 U.S.C. § 102 (a) as allegedly being anticipated by Toyota *et al.* (Cancer Research, 36:4535-4541 (1999); hereinafter "Toyota") is respectfully traversed.

Applicant respectfully submits that the disclosure in Toyota was derived from Applicant's own work. A declaration under 37 C.F.R. § 1.131 stating that the co-authors on the reference were researchers working under the supervision of Applicant is attached herewith. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(a).

In the event any matters remain to be resolved in view of this communication, Examiner is requested to telephone the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: **December 17, 2001**



Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

USPTO CUSTOMER NUMBER 28213

GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133

Enclosures: Exhibits A and B

EXHIBIT A: CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

10. (Amended) A method for detecting a cellular proliferative disorder associated with CACNA1G, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1or SDC4 [in a subject] comprising:

a) contacting a nucleic acid-containing specimen from [the] a subject with an agent that provides a determination of the methylation state of at least one CpG island of a gene or associated regulatory region of the gene;

wherein the gene is selected from the group consisting of APOB, CACNA1G, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1, SDC4 and combinations thereof and

b) [identifying] detecting aberrant methylation of [regions] a region of the gene or regulatory region, wherein [aberrant methylation is identified as being different when] hypermethylation of a region as compared to the same [regions] region of the gene or associated regulatory region in a subject not having said cellular proliferative disorder[, thereby detecting a cellular proliferative disorder in the subject] is indicative of a cellular proliferative disorder.

EXHIBIT B: CLAIMS AS THEY WILL STAND UPON ENTRY OF THE AMENDMENT

10. (Amended) A method for detecting a cellular proliferative disorder associated with CACNA1G, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1or SDC4 comprising:

a) contacting a nucleic acid-containing specimen from a subject with an agent that provides a determination of the methylation state of at least one CpG island of a gene or associated regulatory region of the gene;

wherein the gene is selected from the group consisting of APOB, CACNA1G, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1, SDC4 and combinations thereof and

b) detecting aberrant methylation of a region of the gene or regulatory region, wherein hypermethylation of a region as compared to the same region of the gene or associated regulatory region in a subject not having said cellular proliferative disorder is indicative of a cellular proliferative disorder.

13. The method of claim 10, wherein aberrant methylation comprises hypermethylation when compared to the same regions of the gene or associated regulatory regions in a subject not having the cellular proliferative disorder.

14. The method of claim 13, wherein the regions comprise regulatory regions of CACNA1G.

15. The method of claim 14, wherein the regions comprise regions 1-8 of CACNA1G.

16. The method of claim 15, wherein the regions comprise regions 1-2 of CACNA1G.

17. The method of claim 15, wherein the regions comprise regions 5-7 of CACNA1G.

18. The method of claim 15, wherein the regions comprise regions 4 and 8 of CACNA1G.

19. The method of claim 10, wherein the agent is a pair of primers that hybridize with a target sequence in the gene or associated regulatory region of the gene.

20. The method of claim 19, wherein the primers hybridize with a target polynucleotide sequence having the sequence selected from the group consisting of SEQ ID NO:55-103 and SEQ ID NO:104.

21. (Amended) The method of claim 20, wherein the primer pair is selected from the group consisting of SEQ ID NO:1 and 2, SEQ ID NO:3 and 4, SEQ ID NO:5 and 6, SEQ ID NO:7 and 8, SEQ ID NO:9 and 10, SEQ ID NO:11 and 12, SEQ ID NO:13 and 14, SEQ ID NO:15 and 16, SEQ ID NO:17 and 18, SEQ ID NO:19 and 20, SEQ ID NO:21 and 22, SEQ ID NO:23 and 24, SEQ ID NO:25 and 26, SEQ ID NO:27 and 28, SEQ ID NO:29 and 30, SEQ ID NO:31 and 32, SEQ ID NO:33 and 34, SEQ ID NO:35 and 36, SEQ ID NO:37 and 38, SEQ ID NO:39 and 40, SEQ ID NO:41 and 42, SEQ ID NO:43 and 44, SEQ ID NO:45 and 46, SEQ ID NO:47 and 48, and SEQ ID NO:49 and 50.

22. The method of claim 10, wherein the nucleic acid-containing specimen comprises a tissue selected from the group consisting of brain, colon, urogenital, lung, renal, prostate, pancreas, liver, esophagus, stomach, hematopoietic, breast, thymus, testis, ovarian, and uterine.

23. The method of claim 10, wherein the nucleic acid-containing specimen is selected from the group consisting of serum, urine, saliva, blood, cerebrospinal fluid, pleural fluid, ascites fluid, sputum, stool, and biopsy sample.

24. The method of claim 10, wherein said cellular proliferative disorder is selected from the group consisting of low grade astrocytoma, anaplastic astrocytoma, glioblastoma, medulloblastoma, gastric cancer, colorectal cancer, colorectal adenoma, acute myelogenous leukemia, lung cancer, renal cancer, leukemia, breast cancer, prostate cancer, endometrial cancer and neuroblastoma.